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SPECIAL REPORT

ANTI-HISTAMINIC DRUGS*

William A. Howard, M.D.

The increasing number of potent anti-histaminic and anti-allergic drugs now available has prompted a brief review of these compounds with a view to clarifying their use in allergic patients of pediatric age.

HISTORICAL BACKGROUND

In the study of human allergy, it is readily apparent that many types of antigens may produce the same clinical response. Asthma due to horse serum is indistinguishable from asthma due to ragweed pollen. The response is identical even though the antigens are different chemically and biologically. It is noted also that a given antigen, such as ragweed, may attack more than one organ or tissue in the body, the tissue thus attacked being designated as the "shock organ." Ragweed pollen produces hay fever when the nasal mucosa is the shock organ, and asthma when the bronchial mucosa is involved. It is logical to assume that there might be found some common denominator in these reactions to explain the varied manifestations of allergic diseases.

Since the discovery of histamine in the various tissues of the body, and the demonstration of the similarity of histamine reactions to anaphylaxis and allergy, this drug has been suggested as the common denominator sought for. The role of histamine in anaphylaxis rests on much firmer ground than it does in the naturally occurring allergies of man. While there is no valid argument against the evidence that histamine constitutes a potent factor in anaphylaxis, Feinberg observes that there is likewise some justification for the assertion that not all the manifestations of allergy can be explained on the basis of histamine activity. The complexity of the problem may be inferred from an experiment first performed by Schild, and later confirmed by Cooke. Utilizing the Dale technique of suspension, in a tissue bath, of the uterine horn of a guinea pig sensitized to ragweed pollen, the smooth muscle was repeatedly shocked and forced to contract by the addition of histamine to the bath, until finally no response was obtained, histamine remaining in the bath. After complete relaxation of the uterine horn, ragweed antigen was added to the bath, and prompt contraction occurred. The same result was obtained with atropinized muscle. Conclusions drawn were that "either histamine released from the cell had a different reaction from that of histamine applied to the surface of the cell, or it plays only a secondary part in anaphylactic shock."

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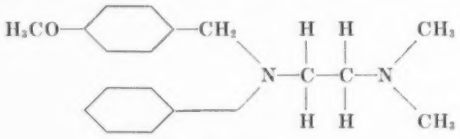
Nevertheless, histamine is now more or less generally accepted as at least a potent factor in the allergic reaction, and many schemes have been devised to try to block or otherwise interfere with the histamine response. Earlier efforts included the use of histamine base in small amounts in an attempt at specific desenitization, and later the employment of histaminase, a naturally occurring enzyme supposed to neutralize or destroy histamine. Neither of these methods have been successful. Still later histamine was combined with despeciated horse serum to form a histamine azo-protein, in the hope that such a compound would be better able to stimulate the formation of antibodies against histamine. Without presenting the evidence it may be safely stated that these methods have offered little in the way of therapy, and there is no apparent basis for the clinical use of these substances at present.

The amino acids, histidine, cysteine, and arginine were shown to have histamine-inhibiting properties, but were insufficiently active, and too toxic for use in man.

The current group of anti-histamine compounds have as a common action the ability to replace or displace histamine already attached to the cell. The earliest of these was synthesized in 1933 by Fourneau and Bovet, but it was not until 1942, when the so called Mosnier compounds were introduced, that really safe and effective anti-histaminics were made available. Since that time many new effective French and American compounds have been given thorough therapeutic trials. It is now possible after five years to compare and to formulate some rules for their use. The new anti-histaminics are not to be confused with the sympathomimetic drugs such as epinephrine and ephedrine. These drugs have no appreciable action on the immuno-chemical mechanisms involved in the antigen-antibody reaction. They owe their anti-allergic effect primarily to vasoconstriction and do not interfere with the use of anti-histaminics.

ANTI-HISTAMINIC COMPOUNDS

1. *Neoantergan* (N-p-methoxybenzyl-N-demethylaminoethyl-amino- alpha-pyridine) was one of the earlier compounds of the Mosnier group investigated for anti-histaminic activity. Since it was more effective and less toxic than its predecessor Antergan, it has replaced the latter for clinical

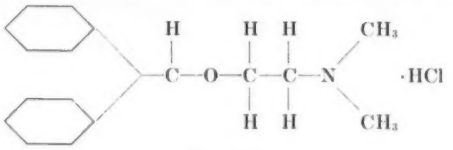


Neoantergan

use. This compound exhibits a marked protective action against histamine shock in the guinea pig, greater than either benadryl or pyribenzamine but there is no such wide variation in anti-anaphylactic and anti-allergic activity. Clinical studies have indicated that results are quite similar to those of the other anti-histaminics to be described.

The drug is available in 25 and 50 milligram tablets and the effective daily dose range is from 100 to 400 milligrams. It is reported that side reactions of drowsiness, lethargy, and dryness of the mouth are milder and less common than with some of the other anti-histaminics.

2. *Benadryl* (Beta-dimenthylaminoethyl benzohydryl ether hydrochlor-



Benadryl
(Diphenhydramine)

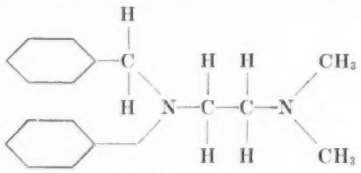
ide) was one of the first anti-histamine compounds made available for use in this country. The drug is soluble in water, and a wheal produced by a 1:500 solution of benadryl exerts a local anesthetic action on the order of procaine 1:200. Stronger solutions are irritating and may cause sloughing.

Extensive clinical trial indicates that benadryl is very effective in urticarial dermatoses, with relief afforded 80 per cent of patients treated. In atopic dermatitis benadryl was effective in relief of itching but did not influence the course of the disease except to eliminate trauma. Results in hay fever and perennial rhinitis have varied widely, but have averaged 50–75 per cent good results. Little benefit is reported in bronchial asthma, especially in those with an associated infectious element. Spirometric measurements of vital capacity before and after benadryl have failed to give evidence of improvement consistent with the occasional subjective benefit reported.

The drug is administered in dosages up to 2 mg. per pound of body weight per day. The individual dose varies from 10 to 50 milligrams, and the total daily dose may be as much as 200 to 300 milligrams. The drug is administered orally in liquid or capsule form but may be given intravenously or intra-muscularly, though these latter routes are not recommended. The elixir contains 10 milligrams per dram, while capsules contain either 25 or 50 milligrams each.

Side reactions include drowsiness, lassitude, dizziness, confusion, amnesia, weakness, dryness of the mouth and nose, nausea, insomnia, and occasionally aggravation of symptoms. These reactions have been reported in greater or less degree in over half the patients treated.

3. Pyribenzamine (N^1pyridyl-N^1Benzyl-N-dimethylethylenediamine) dif-



Pyribenzamine

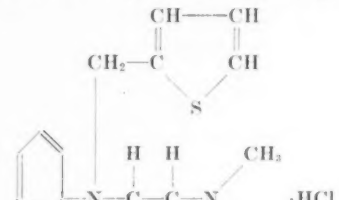
fers from Neoantergan only by the omission of the methoxy group. This drug has been investigated thoroughly and numerous reports are available concerning its efficacy.

In general, it follows the pattern of the other anti-histaminics, and gives best results in urticaria and allied dermatoses. Depending on the dosage employed and the thoroughness of treatment 75–95 per cent of patients obtain relief. In acute and chronic dermatitis, only the pruritis is benefited, and pruritis valvae also responds well. In hay fever relief has approximated 80 per cent, and in allergic rhinitis 65 per cent. Sneezing and local irritation responded best, while nasal blocking was influenced less. When pyribenzamine was used in combination with specific desensitization relief was reported in as many as 95 per cent of patients. Nasal blocking due to vasoconstrictor rebound was relieved promptly. Benefit in asthma has been reported in 25–50 per cent of cases, but is slow and incomplete. Asthma accompanying hay fever or associated with infection is rarely helped.

The drug is available in scored tablets of 50 milligrams and in an elixir containing 20 milligrams per dram. Total daily dosage is the same as for benadryl. It has also been used as a 2 per cent ointment for topical application. Pyribenzamine in combination with ephedrine or aminophyllin is reported to be more effective than when used alone.

Side reactions, identical with those of benadryl, were reported in 25 per cent of patients and were usually mild.

4. *Thenylene hydrochloride* (N,N-dimethyl-N^1-(alpha-pyridyl)-N^1-(al-



Thenylene hydrochloride

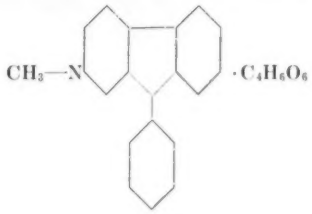
pha-thenyl) ethylenediamine hydrochloride) is similar in composition and action to the other anti-histamines. Clinical experiences with this drug are essentially in accord with results obtained with the others. Greatest clinical improvement was noted in urticaria and hay fever, and least with asthma. The total percentage of patients benefited was 67 per cent which approximates the general average.

Side reactions occurred in 20 per cent of patients and were similar to those previously enumerated. Unpleasant reactions usually disappeared in 4 or 5 days if medication was continued. The drug is available in 50 milligram and 0.1 gm. tablets, and dosages are approximately the same as for the other anti-histaminics.

5. *Nec-ohetramine* (N,N-dimethyl-N^1-p-methoxybenzyl-N^1(2-pyrimidyl) ethylendiamine hydrochloride) is a soluble anti-histaminic, stable in aqueous solution, with a low toxicity. Results of clinical trials with this drug followed in general the patterns previously described. Benefit was reported in 65 per cent of a large series of cases of many varieties of allergic manifestations, but the degree of relief was less than reported for pyribenzamine and benadryl. The incidence of side reactions was low, only 10.9 per cent, and included nervousness, nausea, and insomnia, as well as some of the more common reactions. It was obviously well tolerated, apparently more so than many of the other drugs tested.

The drug is available in 25, 50, and 100 milligram tablets. Dosages approximate those previously described.

6. *Thephorin* (2-methyl-9-phenyl-2,3,4,9-tetrhydro-1-pyridindene) is



Thephorin

used in the form of the hydrogen tartrate salt, is slightly soluble in water, and a 2 per cent aqueous solution has a pH of 5. Thephorin relaxes smooth muscle spasm induced by acetylcholine, barium, and histamine, and has been found to possess a fairly potent local anesthetic action.

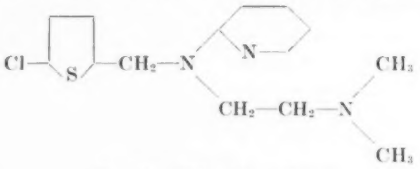
Clinical experience with the drug indicates that benefit is experienced by 65–70 per cent of all patients treated, and that individual allergic conditions respond in about the same proportion as for the other anti-histaminics.

Side effects most commonly noted were dryness of the mouth and in-

somnia, while drowsiness was uncommon and occurred only with high dosages.

The drug is available in tablet and liquid form, and the dosage is the same as for the other drugs.

7. *Tagathen-Chlorothen citrate* (N,N-dimethyl-N¹(2-pyridyl)N¹-(5-chloro-



Tagathen-Chlorothen Citrate

2-thenyl)-ethylenediamine citrate) has been reported to give results equal in percentage to the other anti-histaminics. Thirty per cent of patients showed side reactions, none severe. The level of dosage required for relief was from 100 to 200 milligrams daily, which was somewhat smaller than the requirement of other drugs in this group.

The drug is available in 25 mg. tablets for oral administration.

8. *Decapryn succinate*—2(alpha-(2-dimethylaminoethoxy)-alpha-methyl-benzyl)-puridine succinate. This drug has recently been reported to be another effective anti-histaminic and anti-allergic drug. Its principal point of difference from the others described is its soporific action, greater than Pyribenzamine, but probably less than Benadryl in therapeutic doses. Side reactions occur in 34 per cent. Effective dosage varies from 12.5 to 50 milligrams repeated as necessary, and a small initial dose is recommended.

9. *Hydrillin.* This drug is a combination of diphenhydramine (Benadryl) and aminophyllin. The combination of these two drugs is reported to be more effective than the use of the anti-histaminic alone, especially in the management of asthma. Hydrillin is available in tablets containing 25 milligrams of diphenhydramine and 100 mg. of aminophyllin.

10. *Antistine* (2-phenyl-benzylaminomethyl-inidazoline hydrochloride) is an anti-histaminic with an effectiveness on the order of that of neohetramine, although somewhat larger doses are required. The recommended dosage (adult) is 100–200 milligrams three times daily, with proportunately smaller doses in children. The drug is available in 100 milligram tablets. For control of ocular allergy and the ocular manifestations of hay fever antistine is recommended in a 0.5 per cent solution for instillation into the eye.

11. *Trimeton* (phenyl-(2-pyridyl) beta-N,N-dimethylaminoethyl) methone) is reported to be effective in much smaller dose than the other anti-

histaminics, the adult requirement being 25 milligrams. (one tablet) three times daily. It has the same range of usefullness as the other drugs of this category.

COMMENT

As an adjunct to therapy in the allergic diseases of man, the anti-histamine compounds have been found most effective in urticaria (both acute and chronic), angineurotic edema, serum sickness, dermographism, and allied dermatoses. The itching of pruritis vulvae, atopic dermatitis and some forms of contact dermatitis also are reported as responding well. In hay fever and allergic rhinitis, results have been less spectacular, but encouraging. The results have been uniformly disappointing in asthma, especially cases associated with hay fever, or where there is an infectious element. Success in the treatment of the other less common allergic states has been reported in varying degrees. Nasal blocking due to vasoconstrictor rebound after excessive use of nose drops responds promptly. These drugs have also been administered prior to giving desenitization injections in order to lessen the danger of constitutional reactions.

Side reactions are neither severe nor serious as a rule, and include drowsiness, dizziness, lassitude, nervousness, or insomnia, dryness of the mouth, nose, or throat, headache, burning on urination, gastric irritation, hypotension, diarrhea, and occasionally an increase in allergic symptoms. One or more of these side effects may be seen in approximately 25 per cent or more of patients taking these drugs. These unpleasant symptoms disappear promptly when the drug is discontinued, but generally become less bothersome even if the drug is continued. There is some evidence that anti-histaminics may produce alteration in the electroencephalogram (sporadic increased fast activity superimposed on normal alpha rhythm) while the drugs are actually being administered.

It has been the experience in this clinic that many of the pediatric allergy patients referred to the clinic have failed to respond to anti-histaminics because of insufficient dosage, and failure to try more than one of the drugs. Too often the child's dose is found to be in the neighborhood of 0.5 to 1.0 milligram per pound per day, with no further attempt to regulate the size or spacing of doses to secure maximum benefit. Children as a rule tolerate these drugs quite well, and if they are administered with due caution, daily doses of 2 or 3 mg. per pound may be given if required. Spacing of individual doses is very important if maximum effect is to be secured. It is not sufficient especially in treatment of urticaria, serum sickness, and related conditions, to prescribe a definite dose at specific time intervals. In the acute phase we often find that a rather well tolerated dose of the anti-histaminics chosen will give relief for only 2 or 3 hours,

and that an additional dose will be required at the end of this interval. Giving larger doses to prolong the effect only results in the appearance of unpleasant reactions. As an example, 25 milligrams of the drug given every three hours might produce adequate relief with a minimum of side reaction whereas 50 milligrams every 6 hours would produce irregular relief, with intervals of return of symptoms, and the umbility of side reactions.

The most notable side effects in children are sleepiness, lassitude and vomiting. These manifestations are not serious and will disappear when the dosage is reduced or the drug discontinued. Mild reactions are not considered as contraindication to continued administration of the drugs.

The anti-histaminic compounds represent a useful addition to the therapy of allergic state in general, but it must be emphasized that the benefit obtained is purely symptomatic and temporary and does not otherwise alter the outcome of the disease. It is important to remember that the allergic patient must continue his allergic management including specific hyposensitization where indicated, since the combined form of treatment may give results which are superior to either routine when employed alone. In general, toxic effects are mild, and fairly easily controlled, and do not necessarily constitute a contra-indication to the continuance of anti-histaminic medication. Remote or late toxic effects have not been noted to date, but Feinberg points out the possibility that the anti-histaminics may in some way be found to interfere with the long term production of immunity in specific therapy. It is agreed that none of the drugs so far studied is ideal, but since there may be factors in addition to histamine involved in the allergic reaction, even the most potent anti-histaminic may fail.

FEVER OF UNKNOWN ORIGIN

Case Report No. 135

Morris Tandeta, M.D.* J. B. 36-6844

The patient, a 12 year old colored male, was admitted to Children's Hospital on December 22, 1947 with the chief complaint of high fever of 5 days' duration. He had had a cold, cough, sore throat for about one week. Five days prior to admission he began to vomit and was feverish, so a private physician was called in to see him. A "brown" medicine was prescribed every 4 hours, but the cough, vomiting and fever persisted. Two days before admission he began to have intermittent epigastric pains. It might be mentioned here that the informant was the father whose reliability is questionable.

Past history was essentially negative except that the patient had had pneumonia twice. Family history was non-contributory.

Physical examination revealed an acutely ill, dehydrated, toxic 12 year old colored male. The temperature was 104°. The neck was not rigid. There was an encrusted discharge in both nostrils; the pharynx was inflamed; the tonsils were cryptic. Chest findings were shallow respirations, harsh breath sounds with most rales audible in the lower half of the left lung field and axilla. There were occasional coarse moist rales in the right base with depression of breath sounds in the right apex. The blood pressure was 110/65. Heart rate was rapid but there were no murmurs. The abdomen seemed voluntarily rigid and there was generalized tenderness on deep palpation. Rebound tenderness was equivocal. There was slight diastasis recti. Rectal examination revealed tenderness bilaterally.

The hemogram was as follows: Hemoglobin 11 grams with 2,550,000 red blood cells and 24,200 white blood cells with 59% neutrophils, and 40% lymphocytes. The urine was cloudy with 160 mgm. albumin, 2 plus acetone and microscopic examination showed a large number of fine and coarse granular and epithelial casts with a moderate number of epithelial cells. There were only rare white blood cells.

The impression on admission was bilateral bronchopneumonia, so the patient was placed on 50,000 units of penicillin every 3 hours, intravenous fluids, and aspirin grains 5 symptomatically.

Blood culture taken on admission later showed no growth. Old Tuberculin was negative after 48 hours. Throat smear revealed a preponderance of gram negative bacilli and the throat culture revealed non-hemolytic streptococcus, hemolytic staphylococcus aureus, and N. catarrhalis. The temperature stayed up around 103°–104° and during the night of December

24–25 the temperature rose to 105°. He was given a cooling bath, aspirin, and penicillin was upped to 100,000 units every 3 hours. The lung findings were now mostly in the right base with only a few coarse moist rales in the left base. The cough had become rather severe and paroxysmal in nature. The abdomen was slightly distended, making examination quite difficult. Another throat culture taken at this time revealed hemolytic Staphylococcus albus.

The patient on direct questioning admitted to contact with a dead rabbit about two weeks previously. On December 26, he was seen by a member of the visiting staff who suggested a trial of Streptomycin therapy. Since the sputum contained rusty streaks, daily specimens were collected for acid fast staining and culture. The white count was down to 17,000 with 62% polys. The urine specific gravity was 1.004, albumin 30 and microscopically still showed a large number of epithelial cells, occasional epithelial and coarse granular casts, rare waxy casts, rare white blood cells.

Streptomycin, 200,000 units every 3 hours, was instituted. Blood culture was repeated and later reported negative. A cough plate for pertussis made because of the development of a cough and inspiratory whoop was reported as negative.

Urine culture on December 29 after he had been on Streptomycin 2 days was negative for growth. Sputum smear from concentrated specimens was negative for tuberculosis. On December 30, a cough plate was repeated and was reported negative.

The patient continued to run a high fever, so aspirin, grains X every 4 hours, was given beginning December 29th for about 5 days, and this tended to keep the temperature down around 101° but on discontinuing aspirin the temperature again rose to 104°. Weight was maintained between 61 and 62 pounds consistently. Streptomycin was discontinued after a therapeutic trial of 5 days on the 31st of December.

In the meantime the patient appeared to improve somewhat clinically, the cough lessened, and the sputum was thin, white, and frothy.

On January 4, 1948 penicillin was discontinued. The lungs were now clear to auscultation, heart rate was 120 per minute, but generalized deep abdominal tenderness was still present, most marked in the flanks. Since the urine showed white blood cells, casts, albumin, intravenous pyelography was ordered. The following laboratory data were also obtained: Prothrombin time was 80% of normalcy; cold agglutinins were not demonstrated; non-protein-nitrogen 27 mgm.%. Repeated blood cultures and febrile agglutinations were negative. Urine culture revealed hemolytic Staphylococcus aureus, which was considered a contaminant. The EKG was normal. Heterophile agglutination was negative. Pasteurella tularensis revealed no agglutinations. Sedimentation was 32 mm/hr. cor-

rected. Sickling trait was negative. There were 8,600 white blood cells with 58% polys.

Finally on January 9, smears were reported positive for acid fast bacilli. Cultures of sputum for acid fast have not yet been reported. P.P.D. #1 done on January 14 was 2 plus after 48 hours.

After a transfusion of 350 cc. of whole blood on January 14, 1948, the white-cell count was 5,600 with 61% polys, and the red-cell count was 3,600,000. Urinalysis revealed a specific gravity of 1.017, negative albumin, and only a few white cells and granular casts microscopically.

DISCUSSION

Isidore Lattman, M.D.: An x-ray of the chest taken on the 23rd of December at the time of admission revealed a good deal of disseminated infiltration throughout both lung fields suggestive of bilateral bronchopneumonia although because of the concentration and appearance of the lesion at the roots, the suggestion of tuberculous infiltration was advanced. The concentration of the pneumonitis in the region of the hilii on follow-up films taken on the 31st of December and the 5th of January without any significant resolution of the peripheral infiltration increased the impression of tuberculous origin and despite the inconclusive clinical picture, primary tuberculosis appeared to be the best possibility. (Fig. 1)

In many instances it is impossible to differentiate atypical bronchopneumonia of virus origin from pneumonitis of tuberculous origin on a singlt film of the chest. The clinical course and findings must serve at the time of the first film to differentiate the two. Not infrequently, however, the roentgenologic impression becomes stronger for one or the other after a check film is taken several days later.

Richard H. Todd, M.D.: This patient was admitted during the season when acute respiratory infections were prevalent. The history was not too accurate but he was ill at least 5 days before being admitted to the hospital. His fever, cough and rales in both lungs pointed pretty definitely to a respiratory infection. Sulfa and penicillin did not alter the fever although some of the chest signs cleared up. The tuberculin test on admission was negative. This may have been due to faulty technique in doing the tuberculin or if this is a primary lesion which I believe it is, the elapsed time from the onset to the test may not have been sufficient to develop skin sensitivity.

When the tuberculin test was negative and the pulmonary condition continued in spite of chemotherapy, other less common conditions were investigated. It was possible to elicit a history of handling a rabbit to make tularemia a possibility. The cough he had and the marked leucocytosis

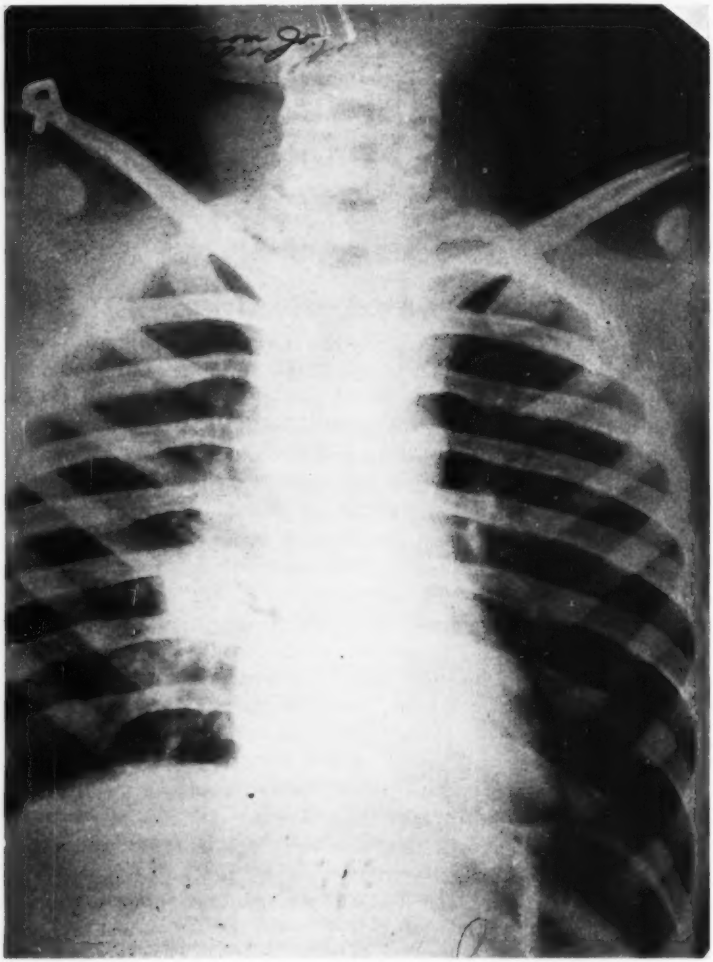


FIG. 1. J. B. Perihilar infiltration with some localized areas of increased density at the roots suggestive of early calcification. There is some infiltration extending from this region into the middle thirds of the right lung field with some compensatory emphysema in the left.

suggested pertussis but both were disproved by culture and agglutinations. The leucocytosis was against a virus infection of the lungs.

We repeatedly came back to tuberculosis in spite of the original negative tuberculin and several negative sputa.

Before a definite diagnosis was made, streptomycin was tried empirically but without definite effect. Aspirin seemed to do as much good for the fever as any of the other drugs.

One complication which baffled us for a short while was abdominal pain and bilateral tenderness. This proved to be due to fecal infarctions which were relieved by numerous enemata. Another finding that confused the picture was the persistence of albuminuria and casts.

Persistence and interest finally solved the problem. The boy was not very toxic in spite of this persistent fever and every few weeks we would send sputum to the laboratory for acid fast bacilli. Another tuberculin test was done 3 weeks after admission and it was found to be positive. A few days later sputum was found to contain acid fast bacilli and the case was solved. A poor history, negative tuberculin on admission and negative sputa during his first week made the early diagnosis almost impossible.

We feel that the findings, the course and x-ray pictures fit in with the diagnosis of primary intrathoracic tuberculosis. This represents a severe case of primary tuberculosis with the greatest intensity of symptoms at the onset and a gradual disappearance of symptoms in the course of time. This is just the opposite to the picture we see in reinfection where the onset is insidious and symptoms increase in severity later.

The majority of primary infections are relatively mild and unrecognized. It is rare to see such a severe onset particularly in this older age group.

Hypersensitivity as measured by the tuberculin test took less than three weeks to develop. This would be in keeping with a rather severe infection since hypersensitivity develops rapidly where there is rapid multiplication of the tubercle bacilli.

The outlook for recovery seems to be good when we consider the improvement the patient has already made. Streptomycin may be beneficial but did not alter the symptoms during the short period we tried it. Rest, good food, and avoidance of further contacts should solve this boy's immediate problem.

SPECIAL REPORT

ACUTE LARYNGOTRACHEOBRONCHITIS

Edgar P. Copeland, M.D.

This disease is an acute infectious inflammation of the larynx, trachea and bronchi characterized by a profound toxemia, edema of the larynx and adjacent structures and a thick viscid obstructing type of secretion.

While often occurring as a complication of other diseases, notably influenza, scarlet fever, measles and chicken pox, it is very definitely a clinical and pathological entity seen too often as a primary condition. This primary type of the disease, to which I especially wish to direct your attention, often without too much warning descends upon the patient with catastrophic suddenness to bring about a fatal issue in spite of the utmost knowledge and skill. This disease is so potentially serious, the mortality varying with different experiences from 25 to 100 per cent,[1] that it behooves us to refresh ourselves concerning its early manifestations in order that out patients may have the advantages accruing from early diagnosis. It is only in this way that the terrific mortality can be substantially reduced.

Age incidence. Though occasionally met with at any age, the disease is essentially one of the first three years of life and there are a number of factors that conspire to make the early years of etiological significance. In the very young, the anatomy of the respiratory system, with the small caliber of the bronchial components, the imperfectly developed cartilages, the redundance of mucous membrane, the superabundance of lymphoid tissues and the extreme vascularity of all structures, is of great importance.

Then, too, in the same period, the natural immunilogical mechanisms have had little time to operate, except perhaps as in the case of diphtheria where they have been artificially stimulated. Consequently few immunities exist to offer even a slight resistance and the defensive reaction of lymphoid tissues to pathogens is often detrimental rather than helpful.

Early life is likewise a period in which certain nutritional or deficiency disorders are prone to be encountered. One of the important ones, rickets, perhaps in sub-clinical form is characterized in part by the vulnerability of the mucous membranes to infection. Certainly associated tetany could contribute to the element of spasmodic obstruction observed in the disease under consideration. The hypochromic anemias so common in infancy make their contribution to and increase the susceptibility of infants to infection. Dentition, with its associated pathology in and about the mouth, nose and pharynx offer portals of entry for infection, as witness the common association of acute tonsillitis with this supposedly normal physiologic process.

And finally, to further increase the hazards, the infant and young child is constantly the recipient of ill-advised but well meant handling and contacts that serve no purpose other than the gratification of some adult emotions.

Seasonal incidence. It must be a matter of common knowledge that the incidence of colds increases with the advent of cold weather when the heating device in the home assumes its functions. Not even modern heating systems provide for an adequate humidification of the atmosphere in homes once the heat goes on, and with the relative humidity at or below 20, the desiccation of mucous membranes proceeds to the detriment of the occupants. In this area, the winter season with its sudden fluctuations in temperature and humidity is a definite predisposing factor to respiratory disorders.

Infecting Agent—Bacteriology. There is unanimity of opinion as to the bacteriology of this condition. The streptococcus haemolyticus is the significant organism in the overwhelming majority of cases.

In the largest series of cases of this character that I have been able to find in the literature, that of Neffson and Wishik from the Willard Parker Hospital, New York City,[2] 28 per cent of 727 cases, after deducting 261 instances of diphtheritic infection, showed strep H. in pure culture from laryngeal, tracheal and bronchial secretions. In the same series

Streptococcus viridans	18%
Staphlococcus aureus	5%
H. Influenza	1%
Some type of Streptococcus alone or combined	92%
Streptococcus haemolyticus alone or combined	70%
Streptococcus viridans alone or combined	51%
Staphlococcus aureus alone or combined	28%

In this same report, it is interesting to note that diphtheria bacilli were reported in 8 per cent of the aforementioned cases with the patients showing negative Schick tests and no evidence of clinical diphtheria; evidently carriers. While the clinical history and pathology of acute laryngotracheobronchitis is quite different from that of diphtheritic croup, a demonstration of diphtheria bacilli in the patient's respiratory tract would demand that he be given the benefit of the doubt therapeutically.

John A. V. Davies reports a small series of cases, 50 per cent of whom were under two years. He reports the staphylococcus as the predominant organism in the first two years and the streptococcus more common thereafter.[3]

Chevalier Jackson, the great master of bronchoscopy, has found the Influenza bacillus the causative factor in 3 to 5 per cent of his cases, but

considers the streptococcus H. primarily or secondarily responsible in over 90 per cent.

Incidentally, he reports the mortality in children to be about 70%.[4]

The influenza bacillus (H. Influenza) appears to be assuming a more important role as the study of this disease progresses. Type B. specific serum, already of proven value in the successful treatment of influenza meningitis, is becoming an increasingly important therapeutic agent in the treatment of laryngobroncheobronchitis in which H. Influenza Type B is demonstrated.

Pathology. With the striking uniformity in the clinical course of the primary cases, in spite of the differences in bacteriological findings, one might postulate the possibility of a basic primary infection, possibly a virus, setting the stage for bacteria as secondary invaders. This hypothesis has been advanced by Arden and Duhig.[5] There is an acute congestion of the mucous membranes of the entire respiratory tract as far as they can be visualized by the bronchoscopist. Edema, especially of the entire laryngeal area, is marked and is associated with a secretion, viscid in character which rapidly becomes thicker and more tenacious as the disease progresses, forming mucous plugs that tend to close the lumina of the bronchial tree causing areas of atelectasis, the physical signs of which are often suggestive of pneumonic consolidations. Bronchopneumonia is a constant finding in fatal cases. Cardiac pathology, especially of the myocardium, frequently results from the toxemia and the fatigue resulting from the anoxemia.[6] The kidneys show the changes peculiar to acute infections. There is usually a neutrophilic leucocytosis and evidence of dehydration. Blood cultures are not uncommonly positive, especially in H. Influenza infections.

Symptomatology and Diagnosis. Davies[3] very aptly expresses the problem as follows: "When a physician is called in the night by a mother who says her infant has croup, the chances are that he has croup. It is important to bear in mind, however, that this may be the start of the far more serious acute laryngotracheobronchitis."

One cannot too strongly stress what many observers have already pointed out, the fact, that acute laryngotracheobronchitis may usually be distinguished from simpler and milder forms of respiratory illness by the evidence that the symptoms are progressive and persistent.

This observation is predicated upon either a dependable history or the opportunity to have observed the patient from the onset of his trouble. Confronted for the first time with an infant seriously ill with respiratory obstruction, in grave need of immediate relief, the problem is not too simple, not nearly as simple as the most lucid description might suggest.

Occasionally this disease seems to be superimposed upon an existing

cold, but more often it is a primary condition. Its clinical course runs fairly true to form. The few minutes required in obtaining an accurate history of the illness is time well spent in the patient's behalf. Much of this history may be secured while the preliminary inspection of the patient is being made. It is important to know, if the child is old enough, whether there has been diphtheria immunization. If so, when? And was a negative Schick obtained and how recently? Has the patient been subject to "croupy" attacks? What time of day did such attacks occur and did they respond to simple treatment?

More often the attack is sudden in onset frequently ushered in with a convulsion in the very young or vomiting in the older ones. The temperature quickly rises to 102 or higher with chilly sensations. The voice, crying or spoken, becomes husky, with a croupy cough, dry and incessant in character, that later softens somewhat with the beginning of secretion. A noisy stridor on inspiration begins to be noticable and presently an expiratory wheeze as though both inspiration and expiration were being obstructed. In an incredibly short time this obstruction becomes visually evident in the retraction of the supra-sternal notch, the supra-clavicular spaces and the epigastrium and in the younger infants the tug of the diaphragm on the soft thoracic wall attracts attention. Slight cyanosis as the disease progresses is not as conspicuous as the alarming ashen pallor. Extreme restlessness develops in the younger patients as the obstruction increases and in the older ones there is an evident anxiety. Both of these symptoms may be interpreted as an index of the increasing seriousness of the illness.

As the secretions increase in amount, becoming thicker, stickier and more glue-like in character, crises occur in the form of plugging of larger or smaller bronchial components. It is this blocking of the airways that precipitates the formation of atelectatic areas so often mistaken for areas of pneumonia. When these areas are of sufficient size the shifting of the mediastinum determined with or without x-ray assistance, is helpful in diagnosis. Finally with increasing toxemia and anoxemia, the cough reflex lost, the patient, deprived of the only mechanism with which he could help himself, begins to fail rapidly. Restlessness and anxiety give way to relaxation, the myocardium shows signs of failure, and the fatal termination is not far away.

Saphis[6] at Michael Reese has reported myocardial failure early in the course of acute laryngotracheobronchitis.

The changes in the clinical course of this disease enumerated above, may be a matter of days, but they may likewise be a matter of hours.

Much too often these patients are brought under the care of the physician when the disease has progressed to a point where differentiation from other

disorder of somewhat similar clinical character, which might have been simple in the beginning, has become extremely difficult. Of this nature may be mentioned membraneous croup, foreign body, massive atelectasis. In the excitement and confusion of the moment inaccuracies in the history creep in and every possible assistance should be had. The help of the bronchoscopist is necessary in diagnosis as well as treatment and x-ray is of inestimable value.

The role of the pathologist is indispensable in ruling out diphtheritic infection, in determining the possible existance of a bacteremia and the nature of the infection in the particular case in hand.

The diagnosis is established by the history of sudden onset, the inspiratory stridor and expiratory wheeze, the evidences of obstruction to the airways and the persistent and progressive worsening of the clinical picture.

Prognosis. The prognosis always grave depends upon first of all the age of the patient, getting progressively better with increasing months, and secondly the duration of the illness before treatment is instituted.

Then, too, there must be considered the bacteriology as determined and the presence of absence or bacteremia.

The assistance of a skilled bronchoscopist cannot be overlooked as a factor of the greatest importance in the prognosis in this disease.

Treatment. Prophylactic: Some acute laryngotracheobronchitis can be avoided by a more serious and intelligent regard for a few prophylactic measures. Generally speaking, considerations of non-specific preventive medicine are too lightly held. There are few factors more predisposing to the infections of the mucous membranes than the desiccatingly dry atmosphere of the average overheated home in winter. This is an obsession with me and I cannot emphasize it too strongly.

Definite effort should be made to keep infants and young children from contact with those suffering with upper respiratory infections, however slight. Such an effort will pay dividends.

Treatment. Once the diagnosis is made or strongly suspected, however early in its course, the case is an emergency and should be so handled. If a properly equipped hospital is available, the patient should be immediately hospitalized, where facilities are available to the attending physician, and his consulting bronchoscopist if necessary, for meeting conditions as they arise.

The measures to be adopted will depend upon the condition of the patient on arrival, but the constant attention of competent nursing care is a prime requisite. If seen early before toxemia is evident and obstruction is too marked, relief can be afforded by an excessively humid warm atmosphere. This can be provided with a tent and humidifier, properly ventilated, or in some hospitals by a special room in which most any degree of relative humidity may be secured. If steam only is employed for the

humidification, the room or tent may become depressingly warm, as pointed out by Brennemann.[7] While a certain amount of heat is desirable, humidification can be accomplished with the modern type of humidifier without excessive heat and the room or tent temperature may be kept below 80°F. Some of these patients seem to be more comfortable in an atmosphere with oxygen, but it should be remembered that oxygen is occasionally observed to be an irritant, aggravating the cough. Have the usual ice removed from the oxygen tent apparatus when using it in the colder months.

Smears and cultures from the upper respiratory tract should be made as soon after the admission of the patient as possible and from the larynx and trachea as well if the laryngologist or bronchoscopist has been in consultation. The finding of diphtheria bacilli in smears or cultures, even in the absence of the evidence of clinical diphtheria, calls for the immediate use of a protective dose of antitoxin. Inasmuch as the hemolytic streptococcus and other streptococci play a predominating role in this disease, vigorous measures should be adopted to combat this infection while awaiting laboratory report.

Subcutaneous sodium sulfadiazine or penicillin or both, depending upon the apparent severity of the infection are indicated. In the case of the former the dose, again depending upon the severity of the infection, should never be less than one grain per pound of body weight in the first twenty-four hours, given subcutaneously for the first dose or two and afterwards by mouth if feasible. In the use of sulfadiazine it is better practice to give larger doses over a shorter period than smaller ones over a longer period. A minimum blood level of 10 milligrams should be maintained and checked daily. Daily urine examinations and blood checks should be made as a part of the observation for the possible toxic effects of the medication.

Penicillin should be used intramuscularly, the initial dose being not less than 50,000 units, with 25,000 units every three hours thereafter. I have not seen nebulized penicillin used in this disease, but with a satisfactory nebulizer such as is now available, I can see no reason why it would not be effective providing the airways are not too obstructed. If I were going to employ it, however, I would do so in addition to its use by the intramuscular route, even though it has been demonstrated that therapeutic blood levels may be secured by inhalation. Meanwhile with laboratory reports available, therapy may be more intelligently continued. In the event that Hemophilus Influenzae, Type B as has been demonstrated by the Alexander Method,[8] Type B specific antiserum should be added to the therapy in dose determined by her methods. My own preference for the intramuscular administration of sera in the very young is based upon some rather unpleasant experiences and I do not hold to it as the more

correct method. I find that the safety of the route more than compensates for the slight loss of time. A 25 mg. ampule well diluted with normal saline should be the minimum initial dose to be checked by the serum capsule reaction described by Alexander.

Dehydration must be combatted by attention to fluids orally and by the intravenous or subcutaneous use of glucose and Hartman's solution, when necessary. Nutrition is not usually a serious consideration since the acute phase of the disease is ordinarily of short duration. The cough is a life saving mechanism and care should be exercised in the use of drugs for its relief. It is the patient's only means of assisting himself in moving obstructing secretions from his airways. Sedation for this annoying symptom, but more important, for the extreme restlessness of the early period of the disease may be employed judiciously under constant observation. Atropine and morphine are positively contraindicated.

Each and every one of the foregoing measures should be discontinued only when there is no longer an indication for their use.

Unfortunately we are too often called to see acute laryngotracheobronchitis when it has progressed beyond the stage where favorable response may be expected from the measures previously described alone. This may be a matter of the virulence of the infection, or failure to appreciate the seriousness of the disease either by the parent or the attending physician.

When a patient is presented with the evidence of serious impending obstruction and asphyxia, the first consideration is the opening and maintenance of his airways. It is at this stage of the disease that surgical interference becomes necessary.

The bronchoscopist, who should have been on notice and available from the beginning, at this time should of necessity be called upon for assistance. It is possible that sufficient secretion may be removed by suction through the bronchoscope to give the patient the necessary relief, but visualizing the pathology, there is little likelihood that such procedure could be repeated often enough to tide the patient over his emergency. The surgeon after his first examination will be better able to judge as to what might be accomplished through the bronchoscope alone.

Bronchoscopy failing, resort must be had to more radical interference. Since from the nature and extent of the obstruction intubation is rarely adequate, tracheotomy is the operation of choice.

The urgency of these decisions require that they often be made in less time than it has taken me to tell about them. The complications and sequellae of tracheotomy in the very young do not weigh against the operation in the face of the existing crisis and may be in some measure lessened by making such interference a matter of election, to be done before the patient is in extremis. The low operation is preferred. The relief of the patient after tracheotomy and the removal of obstruction by suction is

dramatic. This relief of the patient, however has not been permanently accomplished, obstructing mucous plugs and crusts requiring the constant attention of the skilled attendant for a varying length of time after the operation. The recurring accumulation, with its resulting obstruction growing less and less in cases progressing favorably, finally yields to the systemic therapy previously described.

I cannot attempt a detailed recital of the operation of tracheotomy or the post operative care, but some phases must be touched upon. It must be evident that the air provided for inhalation through the tracheotomy tube should not only be moist, but warmed above the temperature required for air that is normally heated by passage through the upper respiratory tract. Cold dry air aggravates the inspissation of the secretions and greatly adds to the difficulty of their removal by suction or other means (removal with forceps).

There must be constantly at the bedside of these little patients an attendant skilled in the post operative care of cases of this character, since complications and crises are constantly arising.

To recapitulate the successful treatment of acute laryngotracheobronchitis is predicated upon early diagnosis and with diagnosis an appreciation of the seriousness of the disease that calls for vigorous treatment. Hospitalization of the patient when possible, prompt laboratory investigation of the nature of the infecting organism and the employment of specific remedies when possible. While resort to surgical measures may in consequence be avoided, it is well to share the responsibilities of such cases with the trained bronchoscopist who certainly should be available on short notice. Tracheotomy is a life saving procedure and should be in these cases an operation of election and not one of last resort.

The after care of tracheotimized patients, especially the very young, calls for a high degree of skill and is no signal for the relaxation of measures designed to combat the infection. Atelectatic areas clear when the obstructing factors are removed but pneumonias are not always as responsive and largely contribute to the mortality after the acute phase of the disease has passed.

REFERENCES

1. Davies: New Eng. J. Med. **229:** 179–199, 1943.
2. Neffson and Wishik: Journal Ped. **5:** 433–617–776, 1934.
3. Davies: New Eng. J. Med. **229:** 179–199, 1943.
4. Jackson C. and Jackson, C. L.: Journal A. M. A. **107:** 929, Sept. 19, 1936.
5. Arden and Duhig: Med. J. Australia **1:** 145–150 Feb. 1944.
6. Saphir: Am. J. M. Sc. **210:** 296–301, Sept. 1945.
7. Brennemann: Am. J. Dis. Children **55:** 667–688, April 1938.
8. Alexander, Ellis and Leidy: Journal Ped. **20:** 691, June 1942.

EROSION OF THE TEMPORAL ARTERY COMPLICATING CELLULITIS

Case Report No. 136

J. M. Perret, Jr., M.D. L. S. 48–6607

L. S., a four month old colored female infant, reported to the outpatient clinic at 6 a.m. on July 15th because of a boil which had been present on the right temporal region for several days which had spontaneously ruptured one hour before and was draining sanguinopurulent material. Examination at that time revealed the draining furuncle and a moderate cellulitis of the surrounding tissues. Procaine penicillin, 150,000 units, was given intramuscularly, hot compresses advised and the mother was instructed to return the next day. At 8:15 a.m. the same day the infant was admitted to the hospital because there was bright red arterial blood escaping from the area of infection.

Examination on admission revealed a cellulitis of the right forehead and face with the right eye closed by periorbital edema and bright red blood spurting from a small skin defect in the center of the right temporal region. The bleeding appeared to be coming from the temporal artery which had evidently been eroded by the cellulitis. The temperature was 102°. Physical examination was otherwise negative.

Laboratory examination showed a hemoglobin of 7.5 gms. with 3.1 million red blood cells. The white-cell count was 25,300 with 85% neutrophiles. Urinalysis was essentially normal. A culture from the bleeding point grew hemolytic Staphylococcus aureus. Blood culture was negative.

Two ligatures were placed above and below the bleeding point. Penicillin 50,000 units intramuscularly every three hours and the usual supportive measures were begun. Six hours after admission when the bleeding was apparently under control, a transfusion of 150 cc. of whole blood was given over a 70 minute time interval. About 30 minutes after the transfusion the dressing became saturated with bright blood. A dry pad was placed over the ligated vessel and pressure applied. No further bleeding followed.

During the next 48 hours the temperature came down to normal. Continuous hot compresses were used over the pressure dressing and by the fourth hospital day the cellulitis had completely subsided. The sutures were removed on the fifth day, penicillin discontinued on the sixth day and the infant discharged on the eighth day apparently in good health.

DISCUSSION

Edward Curran, M.D.: Hemorrhage complicating a lesion such as this is not common. It is usually seen when the infection is in the proximity of

one of the larger vessels. The Staphylococci, particularly, produce an exotoxin which kills adjacent cells. When the adventitia and media of the arterial wall has been weakened, the intima is unable to withstand the arterial pressure. Aneurysmal dilatation and rupture follow with consequent hemorrhage. When rupture occurs, the arterial pressure is sufficient to extrude any thrombus present.

The mechanism described above is the cause of the hemorrhage that occurs in infected wounds, particularly in cases of gas gangrene. Hemorrhage from the common and external iliac vessels has been reported complicating appendiceal abscesses. Less serious hemorrhage occurs in cases of typhoid fever, peptic ulcer and tuberculosis.

When accessible, the hemorrhage may be temporarily controlled by tamponade, digital compression or tourniquet proximal to the bleeding point. The method selected depends upon the location of the bleeding point. In many instances, permanent arrest of bleeding can be obtained by proper application of a pressure dressing. However, ligation of the artery is much more secure. An artery in the vicinity of an infected area will be very friable. Ligation at such a point will be very frequently followed by later secondary hemorrhage. For this reason, it is mandatory to ligate the vessel in healthy tissues, at a point where the integrity of the arterial wall is sufficient to support a ligature. If this can not be done, it is safer to control the hemorrhage by pressure. Incision into an infected area, particularly an area where the inflammation has not localized, would result not only in insecure ligation of the vessel but in further spread of the infection.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: D. Joseph Judge, M.D.
Edwin Vaden, M.D.
By Invitation: Fernando Leyva, M.D.

D. Joseph Judge, M.D.

The patient, a 6 year old white male, was admitted to the Children's Hospital on September 28, 1945 with a history of low grade fever, anorexia and malaise of two weeks' duration. At entry the child complained of precordial pain and generalized abdominal discomfort. No other symptoms were noted.

Investigation of the past history revealed that he had had frequent colds and one episode of otitis media. He had had chicken pox and all the standard immunization procedures. The child had been breast fed and its diet had included a balanced regime along with supplementary vitamins C and D. The developmental history was normal.

The family history showed that an older brother, aged 8, had been a patient in this hospital with the working diagnosis of Hodgkin's disease about one year previously. Physical examination on entry revealed a small, thin, chronically ill, white male child with an unhappy facial expression. The posterior cervical, axillary and inguinal nodes were slightly enlarged but not tender or suppurative. The chest was resonant and there were no rales. The heart rate was 110 per minute, the area of cardiac dullness was not enlarged, and there were no murmurs or arrhythmias. The abdomen was slightly protruberant with the liver and spleen firmly palpable about 8 cm. below the right and left costal margins respectively. There was no ascites. The remainder of the examination including the neurological was normal.

During the early hospital stay the child offered no complaints despite the prevailing physical signs. Initial hemogram showed 7.5 grams of hemoglobin with 3.38 million erythrocytes; there were 5,700 leucocytes, of which 72 per cent were neutrophiles, 23 per cent lynphocytes, and 5 per cent eosinophils. The platelet count was 150,000. No malarial parasites were found on thick smear. The urine was within normal limits. Blood cultures were repeatedly negative. Agglutination tests with febrile antigens were negative. Stool cultures were negative for pathogenic organisms. Intradermal tuberculin and brucellosis tests were negative. Histoplasmin skin test in dilutions of 1-10 and 1-1000 were negative.

Chest x-rays showed some mottled infiltration throughout both lung fields from the apices to the bases more marked in the upper half of the right

chest. A later film taken 23 days after admission showed, in addition, calcification at the roots and thickening of the interlobar fissure on the right.

Therapy consisted of blood transfusions, oral and intramuscular penicillin, aspirin and Fuadin. In spite of all therapy, the patient succumbed on his 30th hospital day.

DISCUSSION

Fernando Leyva, M.D.: The outstanding symptoms and findings of this case may well be summarized as a rapidly fatal disease characterized by a persistent, irregular type of fever, hepatosplenomegaly, adenopathy, leukopenia, and pulmonary involvement as evidenced by x-rays.

I should like to consider initially a group of diseases commonly seen in children having some of the findings in this case. In order of frequency, I should like first to discuss tuberculosis. Clinically and radiologically this case is compatible with a hematogenous form of tuberculosis. However, the absence or lack of mention of a contact and a negative tuberculin test are against this disease. It is true that the tuberculin test is occasionally negative in cases of fulminating tuberculosis, but this is the exception rather than the rule.

Next in order are the blood dyscrasias. A leukemia in an aleukemic phase would have some kind of bleeding manifestations and probably would have immature forms of leucocytes and a lower number of platelets. Rarely do you see a normal leucocyte count in leukemia with such an enormous involvement of the liver and spleen. An aplastic anemia of the idiopathic type would show more depression of the bone marrow. Of course, in both instances a bone marrow study is necessary to be completely sure.

What about sub-acute bacterial endocarditis? Here again the negative history of heart disease, both congenital and acquired, and still more important, the repeated negative blood cultures, are strong points to rule out this disease.

Typhoid fever clinically in children may simulate this case; however, the negative cultures and agglutinations constitute presumptive evidence against the diagnosis. On the same basis, typhus fever (endemic), brucellosis and tularemia cannot be seriously considered.

Next, I would say a word about malignancy. Any lymphomatosis may give a picture similar to that seen in this patient, particularly Hodgkin's disease. The latter would probably have a less acute course, more glandular involvement, and perhaps a skin rash. However, I don't believe you can rule out Hodgkin's disease without a biopsy.

There is another pertinent group of diseases, most of them rare, but yet occasionally seen in children. I am referring to the mycotic group. Par-

ticularly I should discuss coccidioidomycosis. The benign form or San Joaquin Valley fever may give a similar picture and fortunately in this form of the disease the course is benign and the patient recovers in a few weeks. Furthermore, the disease is not endemic in this area. Also, there is an absence of the skin rash in this case. More difficult to rule out would be the progressive type of coccidioidomycosis (granuloma type) because of the clinical similarity. Absent in this case is the bone and articular changes with marked abscess tendency common to coccidioidal granuloma. The skin test is valuable but was not performed in this case. The other disease of the group is histoplasmosis. Each complaint and symptom of our patient may be explained by this disease. Histoplasmosis is characterized as an acute, febrile disease with hepatosplenomegaly, loss of weight, anorexia, adenopathy, leukopenia and pulmonary involvement. A very strong point is the finding of calcification in the chest with a negative tuberculin test. The liver and spleen attain enormous proportions in such cases due to a marked proliferation of the reticuloendothelial system. Occasionally the diagnosis is made by the findings of the fungi in the peripheral blood or more likely in the bone marrow. A skin test with histoplasmin would help in the diagnosis but may not necessarily rule out the disease because cases have been reported with negative skin tests in the presence of the infection. The remaining group of the mycotic diseases are much less likely to give such a picture. Just in passing we should mention actinomycosis, sporotrichosis, monoliasis, torulosis, chromymicosis and aspergillosis.

Two protozoan diseases should be included in the discussion of this case. First kala-azar or visceral Leishmaniasis. I have never seen a case, but from the literature it may be identical with this picture. The typical temperature curve of kala-azar is absent in this case. Often even after death the histological diagnosis is not clear and may be confused with other diseases, notably histoplasmosis. The adult form of human toxoplasmosis, particularly the atypical pneumonic form, may have some symptoms in common with our case, but the spleen and liver are never of such size. A neutralization test for toxoplasma would substantiate the diagnosis.

Other diseases producing enlargement of the spleen and liver would include the lipoid storage diseases. Gaucher's disease and Niemann-Pick's disease are more chronic afebrile illnesses and not infrequently associated with neurological signs. The same applies to Hans-Schuller-Christian's disease but here again the absence of bone defects, exophthalmos, and diabetes insipidus is significant in ruling out these disorders.

In summary, I do not believe I can make a definite diagnosis with the data available. I would have wished to have a bone marrow examination and a culture for Histoplasma capsulatum during the patient's life. My primary impression would be histoplasmosis.

NECROPSY FINDINGS

E. Clarence Rice, M.D.: Examination revealed a well developed but emaciated white boy whose eyeballs were sunken. Fine capillary hemorrhages into the skin of the upper thorax and neck with two purpuric areas involving the skin just below the right anterior superior spine of the ileum were noted; also there was some ulceration about the left nostril. On opening the body, fluid was present in all of the serous cavities, 20 cc. in the peripheral sac, 30 cc. in each pleural cavity and 50 cc. in the peritoneal cavity. All lymph nodes were enlarged, gray and firm. The thyroid and thymus were not enlarged. The right and left lungs were four and two and one-half times their normal weights, varying in color from a bright red to a dusky maroon and were firm and homogenous When sectioned, a number of gray nodules were found scattered through the parenchyma. The heart exceeded its normal weight by 50 per cent and was enlarged to the right. On the surface of the right auricle was found a yellow nodule measuring 3 mm. in diameter. The organ appeared normal otherwise. The liver weighed 960 gms. (normal 642 gms.). Numerous yellowish-white to grayish-white miliary areas are found scattered throughout the parenchyma. There was no evidence of caseation. The spleen weighed 660 gms. (normal 50 gms.), measuring 16.5 x 10.5 cm. The lower pole extended 6 cm. below the ribs. The parenchyma was of a deep maroon color and firm with miliary nodules scattered throughout. The stomach, which was dilated, revealed numerous pin-point hemorrhages in its mucosa. The mucous membrane of the gut was hyperemic. In the ileum a number of firm yellowish-gray elevated masses protruded from the mucosa and some were undergoing ulceration. Peyer's patches were also prominent and some were in the process of ulceration. The pancreas was normal. The adrenals were apparently involved in the disease process being somewhat nodular. The kidneys, which were enlarged, were congested and edematous. The ureters, bladder and generative organs appeared normal. The brain and meninges were grossly normal.

Cultures of the cisternal fluid and blood showed Histoplasma capsulatum.

Microscopic examination of practically all of the organs including the bone marrow showed groups of Histoplasma capsulatum. In some there was marked necrosis with many organisms being present in the reticuloendothelial cells. The gastro-intestinal tract and the lymph nodes were involved to the highest degree.

The appearance of the parasites in the tissues has been sufficiently similar to the Leishman-Donovan bodies to cause pathologists sometimes to make erroneously the diagnosis of kala-azar. The parasite produces a yeast-like

growth of small budding cells which grow satisfactorily in blood culture media and blood agar at 37°C. On Sabouraud's medium at room temperature the growth has a white fluffy appearance which later becomes brown.

The increasing frequency with which the diagnosis of histoplasmosis is being made during life and also at necropsy together with the work of Palmer and others in correlating roentgen findings in calcified pulmonary lesions with positive reactors to intradermal injections of histoplasmin in those who are apparently non-tuberculous would indicate that the disease is considerably more prevalent than we had reason to believe years ago and probably has a lower mortality rate than we would be led to believe on the basis of our four patients, all of whom died.

Dr. Judge: Intentionally omitted from the clinical abstract was the fact that four days before death, Histoplasma capsulatum was found in the peripheral blood.

INCIDENTALLY

Dr. Reginald Spencer Lourie is organizing a psychiatric clinic at Children's Hospital. The clinic workers will include, in addition to Dr. Lourie, a psychologist, social workers, and members of the resident staff. Dr. Lourie received his medical education at the Long Island College of Medicine and later was awarded the degree of doctor of medical science by Columbia University. He was research assistant to Dr. William H. Park of the New York City Board of Health Research Laboratories. He had two years of pediatric training and for three years was Research Fellow in Psychiatry, N. Y. State Psychiatric Institute and Bellevue Hospital, N. Y. C. In addition to several years of clinical psychiatry at the Babies Hospital, N. Y. C. and elsewhere, Dr. Lourie has held teaching positions in pediatrics and psychiatry at the University of Rochester School of Medicine. He is a Diplomate of the American Board of Psychiatry and Neurology and a member of several Psychiatric associations. He is the author of a number of papers on psychiatric and neuropsychiatric subjects. He served in the U. S. Navy for three years and was Chief of Neuropsychiatry in several naval hospitals.

On July 1, 1948 Mr. John D. Martin became Assistant Director of the Hospital.

The National Research Grants Division of the United States Public Health Service has granted a sum of $13,000 to extend for an additional year the study on infantile diarrhea which was initiated July 1, 1947 at the Children's Hospital. The antibiotic and diarrheal study team is in the process of evaluating streptomycin, polymyxin and aureomycin in the management of specific and non-specific gastroenteritis in infants and children. Toward this end, a special diarrheal ward and laboratory group have been in operation. Preliminary results of this study are in the process

of preparation and will be published in this bulletin when they are completed.

A sideline study has been the evaluation of the newer antibiotics on other susceptible diseases in infants and children. A preliminary report on the use of aureomycin in the treatment of Rocky Mountain spotted fever will be published shortly in the J. A. M. A. and will be summarized also in this bulletin.

Morris Tandeta, M.D. (Fever of Unknown Origin), whose permanent address is Tennessee, was born in 1919. He attended the University of Chattanooga, and received his M.D. degree from the University of Tennessee in 1943. Following an interneship at Gallinger Municipal Hospital in Washington, D. C., Dr. Tandeta served in the United States Army for 26 months. He has had resident training at the Jewish Hospital in Louisville, Kentucky, and is at present a member of the Resident Staff of Children's Hospital. Future plans are for the practice of Pediatrics in California.

Joseph Maxime Perret, Jr., M.D. (Erosion of the Temporal Artery Complicating Cellulitis) is a native of Louisiana and was born in 1922. He attended Loyola University of the South, and Louisiana State University School of Medicine where he received his M.D. degree in 1943. Dr. Perret served in the United States Navy from 1943 to 1946. He has practiced in New Orleans, Louisiana for approximately one year and is on the Associate Staff of the Hotel Dieu Hospital, New Orleans and is a Visiting Physician at St. Vincent's Infant Asylum, New Orleans. He is on the Resident Staff of Children's Hospital, Washington, D. C., and plans to practice Pediatrics in New Orleans on completion of his training.

Edmund B. Curran, M.D. (Erosion of the Temporal Artery Complicating Cellulitis) was born in Maine in 1916. He attended Brown University and Georgetown University School of Medicine where he received his M.D. degree. Following an interneship at St. Joseph's Hospital in Providence, Rhode Island, Dr. Curran served in the United States Navy. He has had resident training in Pathology at the University of Minnesota, and surgical training at St. Mary's Hospital in Detroit. He is on the Surgical Resident Staff at Georgetown University Hospital, and is at present serving a six months period of training in Pediatric Surgery at Children's Hospital on loan from Georgetown. Dr. Curran plans to practice General Surgery on completion of his post graduate training.

SUMMARY OF THE CHILDREN'S HOSPITAL EXHIBIT AT THE MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS ATLANTIC CITY, NOVEMBER, 1948

Congenital Biliary Atresia

Fernando R. Leyva, M.D.
Howard S. Madigan, M.D.

A survey of the cases of congenital biliary atresia at Children's Hospital from 1941 to 1948 indicates that 19 patients were found to have this anomaly at operation or autopsy. These cases represent 8% of the total admissions for jaundice during this period. The various causes of jaundice in 126 cases are listed in Table I.

Nine of the 18 patients were considered operable, an operability rate of 50 percent. This is in contrast to the operable patients in the series of Ladd and Gross in which only nine of 45 were considered operable, a percentage of 20.

In the nine operable patients some form of anastomosis was performed in six. There was another patient, in whom an exploratory operation was performed but the anomaly not recognized, who succumbed and the actual pathology was discovered at autopsy. Two others died before surgery could be performed.

Five of the six patients in whom an anastomosis was done are living and well from 11 months to 5 years after operation. This is a survival rate of 83.3 percent. This compares favorably with the survival rate of 75 percent in the series of Ladd and Gross. The single fatal outcome was in a patient who, following an anastomotic procedure, developed intestinal obstruction and died three days later.

Table II outlines the type of atresia, the corrective surgical procedure, and the survival period in each of the successful cases.

Three of the other four patients considered to have operable anomalies had atresia of the lower end of the common duct. The diagnosis was not suspected in life but was made at autopsy in two of these. In the third case, in addition to a common duct atresia, there was a large choledochal cyst which was anastomosed to the jejunum. This was the patient who died of intestinal obstruction shortly after operation.

In the fourth of the operable cases with fatal termination, the actual anomaly was not discovered at operation. Autopsy revealed an atresia of the lower end of the hepatic duct with a large cystic dilatation of the duct proximal to the obstruction. It is noteworthy that this was the only

instance of involvement of portions of the biliary system other than the common duct in our series.

Ten cases were either explored and considered inoperable or died without surgery and came to autopsy. In all ten there was complete absence or mere vestiges of the biliary system.

TABLE I

TYPE OF JAUNDICE	CASES	PERCENT
Catarrhal jaundice (Hepatitis)	50	40
Icterus neonatorum*	25	20
Erythroblastosis foetalis	15	12
Biliary atresia	11	8
Familial hemolytic jaundice	3	3
Other hemolytic jaundice	3	3
Luetic	3	2
Miscellaneous	16	13

* This figure is low because Children's Hospital has no newborn service.

TABLE II

PATIENT	ANOMALY	SURGERY	SURVIVAL
J. L.	Atresia, lower common duct	Cholecystoduodenostomy	5 years
M. A.	Atresia, lower common duct	1. Cholecystotomy 2. Anastomosis, gall bladder to lower stomach	2 years 6 months
B. E.	Atresia, lower common duct, with great dilatation	Cholecystojejunostomy	11 months
S. F.	Atresia, lower common duct, with dilatation and rupture	Ligation of duct. Anastomosis, gall bladder to lower stomach	4½ years
J. H.	Atresia, lower common duct	Cholecystoduodenostomy	11½ months

Neurological Residuals Following Pyogenic Meningidites

Vasilios S. Lambros, M.D.
Frank J. Murphy, M.D.
Francis L. Zinzi, M.D.

Although pyogenic meningitis has been studied and reported in most of its phases, little attention has been directed to the residuals following such severe infections of the central nervous system. Interest has been focused

on the effectiveness of various forms of therapy based primarily on whether the patient survived or fell before the onslaught of the infection. While this is important, it is necessarily a near-sighted viewpoint in that any form of therapy should be of sufficient scope to include in its basic protocol the useful functioning of that individual in normal society. It has been the purpose of this study to determine the incidence of residuals resulting from this disease and the hope that the realization of their frequency would lend itself to better use of the specific therapeutic measures available.

It is true that we are in a period of therapeutic transition so that the effectiveness of today's therapy can only be judged in the years to come. Therefore this is a preliminary report of the six year period of 1942 through 1947.

The diagnoses of the cases included in this paper were established by the usual signs and symptoms and confirmed by positive bacteriological smear and culture. Thus many cases were excluded on the basis of being secondary to other conditions which allowed invasion of the meninges by direct extension. This latter group included meningocoeles, meningomyelocoeles, fractures of the cribiform plate, compound skull fractures and spontaneous rupture of pyogenic subcortical abscesses.

The incidence of the mortality and neurological residuals are presented on the basis of 231 cases. No follow up examinations, for various reasons, could be obtained in the 88 cases of confirmed pyogenic meningitis occurring during this period and nothing can be stated concerning this group.

In this series of 319 cases, 97 of the patients died during the acute stage of their infection. The number of recoveries, in so far as life was concerned, totalled 222 cases. From this group, 134 children (61%) were examined by a group of examiners including two pediatricians, a neurologist, an otologist and a psychologist to determine the extent of their recoveries. In those instances where indicated an opthalmologist was consulted. From these examinations, 62 patients (46%) were noted to have neurological abnormalities attributable to their central nervous system infection.

Of the three predominating etiological agents, H. influenzae, meningococcus and pneumococcus, the latter has been the most serious offender both in regard to mortality and residuals. As was to be expected the infant group suffered the highest mortality rate and the highest incidence of residuals.

The neurological abnormalities in the order of their frequency have included: Severe group—(1) mental retardation; (2) deafness; (3) major convulsive state; (4) blindness; (5) diplegia; (6) hemiplegia; (7) hydrocephalus; (8) quadriplegia, (9) deaths as a latent result of their infection, Moderate group—(1) hemiparesis; (2) extraocular paresis; (3) ataxia

(flocculonodular syndrome); (4) speech impairment; and (5) lower facial paralysis.

Roentgen Therapy in Ringworm of Scalp (Tinea Capitis) due to Microsporon Audouini

Isidore Lattman, M.D.

Roentgen therapy (temporary depilation) is by far the best method of treatment of ringworm of the scalp (due to Microsporon audouini) at the present time. It is the treatment of choice. The great majority of general practitioners, many of the dermatologists, and even some of the radiologists refuse to use this method of treatment because of the possibility of medico-legal complications due to possible permanent alopecia, burns, etc. We, who have treated a large number of cases at our Children's Hospital, Washington, D. C. in the past twenty years with singular success, have decided to report these cases and describe the method we use which is essentially the same method used all over the country with some modifications.

The treatment has stood the test of time for a period of about forty years. In fact as early as 1897 Freund reported this method of treatment. In 1909 Kienbock's therapy which was improved by Adamson, had become the standard method in use in the United States, the so-called "5 point" method. Doctors Pendergras and Mahoney state that "since 1943, ringworm of the scalp has been epidemic in the eastern seaboard of the United States. MacKae and his associates reported 4,000 cases in New York City and 13,000 cases in Philadelphia in 1945. In Hagerstown, Maryland and adjacent counties, out of a total of 8,657 children examined, 565 (479 boys and 86 girls) were infected."

From the editorial in the Journal of the American Medical Association (September 18, 1948, volume 138, #3) entitled "Hazards of X-ray" we quote the following.

"A therapeutic irradiation that has long been viewed askance by many radiologists is its use for epilation to cure ringworm of the scalp in children. In the early days when equipment was unreliable and measuring instruments unsatisfactory, alopecia was a frequent sequel. Today many radiologists who do have adequate equipment nevertheless refuse to do therapeutic epilations. They feel that the chances that permanent alopecia will result are not negligible and that the blame for such an accident is beyond their willingness to face. This attitude seems less than worthy of our profession. If any patients with ringworm of the scalp need irradiation, then duty demands that one do it if technically equipped, or if not so equipped that one know whither to refer the patient to get it done."

The following paragraph is from an article in "Radiology", April 1948,

Volume 50, Number 4: "A consideration of Roentgen Therapy in Producing Temporary Depilation for Tinea Capitis", by Eugene P. Pendergrass, M.D. and J. Francis Mahoney, M.D., Philadelphia, Pa. "The Advantages of X-Ray Treatment are Multiple.

1. In the proper hands, with adequate equipment, the procedure is painless and so far as we know is harmless to the underlying brain. Permanent alopecia, is not easily produced. If it does occur, and it is possible, we believe that in most instances some other factor than radiation is present. Nevertheless, many physicians are hesitant about employing x-ray therapy because of the possibility of medico-legal complications should permanent alopecia result. We believe that alopecia under such circumstances must be rare, and, therefore, have taken the position that as radiologists we should not withhold x-ray treatment from those who need it for tinea capitis."

We are presenting a series of pictures, graphs and charts which we believe speak for themselves. We do want to state that in twenty years of experience we have had only three bad results. Two of these were permanent alopecia which we cannot explain or account for. We believe that there must have been other factors than radiation which were responsible for the permanent alopecia. We have had one scalp burn and that was our fault. In five cases we had to depilate twice, but these patients similarly showed good results. Recently there has been a report indicating that local application of some new chemicals has been used successfully in curing tinea capitis. However, until this is proven to be so, it would be advisable to continue to use x-ray depilation.